Predictors of ischemic heart disease in patients with depression disorder in the emergency room: a retrospective study

Moriyuki Terakura, Ryuichi Fujisaki, Takaoki Suda
Toshio Sagawa, Tetsuya Sakamoto

ABSTRACT  Depression is well known to contribute to ischemic heart disease (IHD) development. However, IHD is difficult to diagnose in the critical care setting because symptoms are masked when combined with depressive manifestations. We assessed the associations between depression and factors involved in lifestyle-related diseases. The study population was 397 consecutive patients with mental disorders, seen in our emergency room (ER) between May 2009 and May 2010. We analyzed patients with depression (n=269) as compared to other mental disorders (n=128) (Schizophrenia [n=116], Anxiety neurosis [n=8], Dissociative disorder [n=4]) in terms of individual background factors (age, gender, systolic and diastolic blood pressures, any history of IHD, hypertension, diabetes mellitus, hyperlipidemia), white blood cell count and C-reactive protein using logistic regression. When adjusted for age, the hypertension rates were significantly higher in patients with than in those without depression (40.6% vs. 19.7%; p=0.009). In a multivariate analysis, history of hypertension was independently associated with patients with and without depression (p=0.045; odds ratio, 1.97 [95% CI, 1.01-3.89]). Furthermore, the risk of moderate cardiovascular events was significantly higher in hypertensive patients with depression than in hypertensive patients without depression (34.6% vs. 13.0%, p<0.001). In conclusion, the results suggest that depression is significantly frequently accompanied by hypertension and that patients with depression need to be managed as those at an elevated risk for cardiovascular disease.

(JJAAM. 2013; 24: 77-84)
Key words: depression, ischemic heart disease, hypertension

Received on April 13, 2012 (12-039)

Introduction

In May 2009, a full-service emergency room (ER) was established at Teikyo University Hospital to provide primary and secondary emergency care, mainly accepting patients requiring ambulance service to the ER during general outpatient service hours. In the ER, patients with mental disorders were routinely seen for medical examinations. However, in these patients, it can be difficult to diagnose critical diseases, such as cardiovascular disorders, in the ER due to masking of essential symptoms by depressive symptoms. Therefore, patients with mental disorders should receive special attention, particularly patients with depression. Depression and ischemic heart disease (IHD) are both very common diseases\(^1\), and the presence of depression and IHD together worsens outcomes\(^2,3\). Although the association between IHD and depression was thus demonstrated many years ago, there are many unresolved questions about the association between depression and factors involved in lifestyle-related diseases, known to be closely involved in the onset of IHD. The present study was undertaken to identify depression-associated factors of lifestyle-related diseases, including a history of IHD.

Material and Methods

Subjects and Analysis of Objectives

The study population was comprised of 397 consecutive patients with mental disorders seen between May 2009 and May 2010 in the ER at our hospital. The medical records of each patient were checked, and the disease history was taken by interview. Mental disorders had previously been confirmed at the Department of Psychiatry,
Teikyo University Hospital. Using logistic regression, we compared the demographics and medical histories of patients with depression (n=269) to those of patients with other mental disorders (n=128), including schizophrenia (n=116), anxiety neurosis (n=8), and dissociative disorder (n=4). Specifically, gender, systolic and diastolic blood pressures, white blood cell (WBC) count, C-reactive protein (CRP), and histories of IHD, hypertension, diabetes mellitus (DM), and hyperlipidemia were examined.

Patients with and without hypertension were stratified according to the rate of cardiovascular disease, as outlined in the Japanese Society of Hypertension criteria published in 2009. This study was approved by the Ethics Committee of Teikyo University Hospital (Teikyo Ethics Committee Approval No.11-083).

§ Statistical Analysis

Continuous variables were expressed as means ± standard deviations. The two groups were compared using the t-test or Mann-Whitney’s U-test. Intergroup comparisons were carried out using Fisher’s exact test or the Chi-squared (χ²) test. To adjust the data for age, the Mantel-Haenszel test was conducted on nominal scale data with age categories serving as a confounding factor, while binomial logistic analysis was conducted on continuous data. Spearman’s rank correlation coefficient was applied. Associations between depression and other mental disorders in terms of individual background factors (age, gender, systolic and diastolic blood pressures, WBC count, CRP, and histories of IHD, hypertension, DM, and hyperlipidemia) were evaluated using univariate logistic analysis. Subsequently, background factors with P-values less than 0.2 and the presence or absence of depression were subjected to multivariate logistic analysis, and results were expressed in terms of odds ratios (OR) with 95% confidence intervals (CI). Differences with P-values less than 0.05 were considered statistically significant. The SPSS statistical package for Windows, version 11.0.1J (SPSS Inc., IL, USA) was used for all analyses.

Results

The analysis of reasons why the study population visited the ER revealed that mental complaints such as dizziness, palpitations, and shortness of breath were the major factors triggering an ER visit in 67 (24.9%) of the 269 depressed patients and 45 (35.1%) of the 128 patients with a nondepressive psychiatric disease (37 of the 116 patients with schizophrenia, 7 of the 8 patients with anxiety neurosis, and 1 of the 4 patients with dissociative disorder). Table 1 gives comparisons of background factors according to depression status.

<table>
<thead>
<tr>
<th></th>
<th>Depression (+)</th>
<th>Depression (-)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>269</td>
<td>128</td>
<td>-</td>
</tr>
<tr>
<td>Gender (female:male)</td>
<td>205:64</td>
<td>96:32:00</td>
<td>NS</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>56.5 ± 19.4</td>
<td>48.8 ± 17.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>133.3 ± 26.1</td>
<td>125.7 ± 23.2</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>76.5 ± 15.4</td>
<td>77.7 ± 14.3</td>
<td>NS</td>
</tr>
<tr>
<td>History of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD (%)</td>
<td>13.5</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>40.6</td>
<td>19.7</td>
<td>0.009</td>
</tr>
<tr>
<td>DM (%)</td>
<td>13.9</td>
<td>10.2</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>20.3</td>
<td>10.2</td>
<td>NS</td>
</tr>
<tr>
<td>WBC (µL)</td>
<td>7842.2 ± 4027.6</td>
<td>7412.8 ± 2868.8</td>
<td>NS</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>1.42 ± 3.03</td>
<td>1.76 ± 4.24</td>
<td>NS</td>
</tr>
</tbody>
</table>

IHD: ischemic heart disease, DM: diabetes mellitus, WBC: white blood cell, CRP: C-reactive protein.
As shown in Table 2, pertinent data were first subjected to univariate logistic analysis using the presence or absence of depression as the dependent variable and the following parameters as independent variables: age, gender, systolic and diastolic blood pressures, WBC count, CRP, and histories of IHD, hypertension, DM, and hyperlipidemia. Then, dependent variables were subjected to multivariate logistic analysis, and the results are presented in Table 2.

Independent factors with P-values less than 0.2 were age, systolic blood pressure, hypertension, IHD, and hyperlipidemia. In the multivariate logistic analysis, the χ² test yielded a P-value of less than 0.001, the Hosmer-Lemeshow test value was acceptable (0.083), and the discriminatory predictive value was 67.4%, indicating that history of hypertension constituted an independent factor associated with the presence depression (p=0.045; OR, 1.97 [95% CI, 1.01-3.89]).

Fig. 1 illustrates the risk for cardiovascular disease in hypertensive patients with or without the complication of depression. We stratified the patients with hypertension according to the incidence of cardiovascular disease, as outlined in the Japanese Society of Hypertension 2009 guidelines. Patients were divided into 4 groups (none, low, moderate, and high) according to their risk of cardiovascular disease. The percentage of patients allocated to the moderate-risk category was evidently higher in the depression group than in the nondepressive psychiatric disease group (5.5% vs. 3.8%, p<0.001; and 6.8% vs. 23.1%, p<0.001, respectively). However, the percentage of patients allocated to the high-risk category did not significantly differ between the 2 groups (9.8% vs. 6.5%, NS).

**Discussion**

In the current study, we analyzed the association between depression and factors of lifestyle-related diseases. Depression is known to contribute to the onset of IHD, and depression accompanied by hypertension is known as a major factor responsible for the onset of IHD. Other studies have described integral medical therapies for comorbid depression and hypertension to improve patient outcomes, suggesting that comorbid depression and hypertension may contribute to the increased mortality rate in patients with IHD.

Fig. 1 illustrates the percentage of patients rated at each level of cardiovascular risk in the depression group and the nondepressive psychiatric disease group. The risk was rated higher in patients having hypertension or a larger number of risk factors. The percentage of patients having normal blood pressure or grade 1 hypertension (140 to 159/90 to 99 mmHg) or free of cardiovascular risk factors was higher in the depression group, whereas the percentage of patients having grade I or II hypertension (160 to 179/100 to 109 mmHg) or possessing 1 or 2 cardiovascular risk factors (other than DM) was higher in the depression group than

### Table 2. Results of logistic regression analyses.

<table>
<thead>
<tr>
<th></th>
<th>Univariate logistic analysis</th>
<th>P-value</th>
<th>Multivariate logistic analysis</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>odds ratio (95% CI)</td>
<td></td>
<td>odds ratio (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>1.07 (0.52-2.73)</td>
<td>0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.02 (1.01-1.03)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>1.04 (1.02-1.05)</td>
<td>0.011</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.96 (1.01-1.01)</td>
<td>0.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of IHD</td>
<td>2.19 (1.02-4.67)</td>
<td>0.044</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.79 (1.54-9.10)</td>
<td>&lt;0.001</td>
<td>1.97 (1.01-3.89)</td>
<td>0.045</td>
</tr>
<tr>
<td>DM</td>
<td>1.59 (0.78-3.08)</td>
<td>0.213</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>2.23 (1.17-4.27)</td>
<td>0.015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td>1.00 (1.00-1.00)</td>
<td>0.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>0.97 (0.90-1.05)</td>
<td>0.49</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

95% CI: 95% confidence interval, IHD: ischemic heart disease, DM: diabetes mellitus, WBC: white blood cell, CRP: C-reactive protein.
in the nondepressive psychiatric disease group. These findings seem to be consistent with previous reports that depression tends to be associated with lifestyle-related diseases such as IHD and hypertension 1-9), although the percentage of patients allocated to the high cardiovascular risk category was low and did not differ between the depression group and the nondepressive psychiatric disease group in the present study. In this study, the cardiovascular risk was rated as high (high-risk category) in patients having grade 2 hypertension (160 to 179/100 to 109 mmHg) and 2 cardiovascular risk factors or having grade III hypertension (over 180/over 110 mmHg) or possessing 3 or more cardiovascular risk factors. In the depression group, the cardiovascular risk was rated high in 17 patients having grade III hypertension and 3 patients possessing 3 or more cardiovascular risk factors. In the nondepressive psychiatric disease group, the cardiovascular risk was rated high in 7 patients with schizophrenia (grade III hypertension, 5 patients; 3 or more cardiovascular risk factors, 2 patients). Such a low percentage of patients rated as having high cardiovascular risk also seemed to be associated with treatment of hypertension or with age. For this reason, we analyzed the percentage of patients rated at high risk in relation to covariables (presence/absence of hypertension treatment and age categories), but none of these covariables were found to affect the cardiovascular risk assessment (data not shown). Thus, the exact reason is unknown but it seems likely that the low percentage of patients allocated to the high-risk category is associated with the tendency for low blood pressure among the patients enrolled in this study and the insufficient total number of patients studied.

In univariate logistic analysis, for systolic blood pressure was strongly related to depression. Generally, systolic blood pressure increases gradually with advancing age, while diastolic blood pressure rises progressively until approximately age 50 and remains essentially unchanged thereafter. The majority of subjects with hypertension who are over 60 years of age have only high systolic blood pressure 10). Moreover, shear stress on blood vessels has been shown to be increased by elevated pulse
pressure due to systolic hypertension, and the circulation of unstable blood within the vascular system has been associated with the risk of stroke. Our data revealed that systolic blood pressure, rather than diastolic blood pressure, was strongly related to depression in univariate logistic analysis, which may reflect the high number of patients experiencing comorbid depression and IHD before reaching 60 years of age.

The biological mechanism through which depression and hypertension are associated remains unclear. Previous studies have shown that depression contributes to disease and death through immune dysregulation, which is exacerbated by atherosclerotic factors, cardiovascular disease, hypertension, age, and DM. Furthermore, depression is known to occur in patients who experience hypertension mediated by the hypothalamic-pituitary-adrenocortical (HPA) axis. With this chronic imbalance in the autonomic nervous system, hydrocortisone produced by the HPA system induces endothelial injury, subsequently resulting in hypertension and atherosclerosis. Sympathetic activity has also been shown to be involved in the development of hypertension. Chronic sympathetic hyperactivity increases the cardiovascular workload and predisposes the patient to cardiovascular cellular damage. On the other hand, vagal nerve activation is protective against ventricular arrhythmias during myocardial ischemia as consequence of depressed baroreflex sensitivity, and therefore, β-blockers that lower heart rate and reduce heart contractions are expected to effectively suppress the compensatory sympathetic nerve activity which is hazardous to the heart in the long run and are known to decrease all-cause mortality. The mechanism for onset of hypertension and other lifestyle-related diseases secondary to depression has been described above. Regarding the reverse case of patients developing depression secondary to lifestyle-related diseases including IHD, as investigated in the present study, a health survey in the United States revealed the annual odds for the onset of major depressive disorder: 2.00 in patients with hypertension, 2.30 in patients with coronary artery disease, and 1.96 in patients with DM. Inamitsu et al reported that hypertension is likely to be complicated by depression, with the risk for onset of depression being about 3 times the risk in a hypertension-free control group, and that coronary artery disease is also likely to be complicated by depression, with the risk also being about 3 times higher than in a control group.

Regarding the prevalence of lifestyle-related diseases including IHD in Japan, the outline of the national health and nutrition survey for the fiscal year 2010 (published by the Ministry of Health, Labour and Welfare) shows that the prevalence of hypertension among men was 21.5% at age 40 to 49 and 57.5% at age 70 and over, and its prevalence among women was 10% at age 40 to 49 and 57% at age 70 and over. Thus, the prevalence of hypertension was higher than that of DM and hyperlipidemia, and men aged over 70 having DM or hyperlipidemia had a particularly high (about twice as high) prevalence of hypertension. Regarding the prevalence of angina pectoris and myocardial infarction, the same report showed that the prevalence of angina pectoris was 7.5% in men aged over 70 and 3.4% in women aged over 70, and the prevalence of myocardial infarction was 9.3% in men and 6.5% in women of the same age group. Regarding the possible factors explaining the likelihood for the development of depression in hypertensive patients, the report points out the personality characteristic (methodical, earnest and having a strong sense of responsibility) common to hypertensive patients and depressed patients. In addition, it has been reported that stress on blood vessels due to hypertension activates an adrenocortical hormone, leading to activation of HPA axis, thus causing an imbalance in the autonomic nervous system. Thus, the significantly high percentage of depressed patients having a history of hypertension shown in previous reports and the present study seems to reflect: 1) a higher prevalence of hypertension than the prevalence of any other lifestyle-related diseases in Japan; 2) a tendency for hypertensive patients to have a personality characteristic resembling depressed patients regardless of age group; and 3) the close involvement of hypertension-related stress on blood vessels in the etiology of depression.

Stress and insomnia are closely related not only to hypertension but also other lifestyle-related diseases such as hyperlipidemia and DM. There are interactions between lifestyle-related diseases and insomnia, forming a vicious cycle (aggravation of one of them leading to aggravation of the other) that has the potential to induce depression. The onset of depression secondary to IHD has been reported to involve factors such as smoking, unfavorable dietary patterns, and physical inactivity.

In the present study, the prevalence of depression with a history of IHD was lower than the prevalence of depression with a history of hypertension. We cannot rule out that this reflects a difference in the prevalence between these 2 diseases in Japan. However, smoking, un-
favorable dietary patterns, and physical inactivity among patients with IHD have not been analyzed in detail and their involvement in the onset of depression remains unknown. Despite this, the univariate analysis performed during the present study revealed a significant association between IHD and depression, and previous reports demonstrated a 2- to 3-fold higher risk for the onset of depression in patients with IHD, similar to the risk in patients with hypertension\(^{20,21}\). Therefore, care needs to be taken when dealing with patients with IHD regarding a possible complication of developing depression, in a way similar to that used when dealing with patients with hypertension.

In the present study, no significant association between DM and depression was noted. This is probably explained as follows. In the nondepressive psychiatric disease group, DM was seen in 13 (10.2%) patients, all of whom were diagnosed with the nondepressive psychiatric disease schizophrenia. Patients with schizophrenia often have poor health behaviors and medication side effects. Because of this background, DM is considered to be relatively likely to be complicated by schizophrenia\(^{26}\). Such an association between DM and schizophrenia probably resulted in there being no difference in the prevalence of DM between the depression group and the nondepressive psychiatric disease group.

This study had several limitations. First, this study was designed as a retrospective study; the majority of the information used was derived from medical records. For this reason, a detailed assessment of patient personality and other information on individual patients (eg, sleep status) could not be sufficiently carried out. As described above, the onset of depression is closely associated with lifestyle-related diseases, personality and sleep status. It is desirable to analyze personality and sleep status as well in this kind of study.

Second, the average systolic blood pressure was 133.3 ± 26.1 mmHg and therefore did not meet the criteria for hypertension (blood pressure exceeding 140/90 mmHg), which may reflect the predominance of the relatively younger population in our study, where patients with depression averaged 56.5 ± 19.4 years of age and patients without depression averaged 48.8 ± 17.2 years of age.

According to the Japanese Society of Hypertension, the average systolic blood pressure in our study corresponded to the “normal hypertension” category. Despite this, our results demonstrated that among patients in the moderate-risk group for the development of cardiovascular disease, those with depression were more likely to have risk for cardiovascular disease than those without depression. Therefore, attention should be given to risk cardiovascular disease development, even in relatively young patients.

In conclusion, the results from this study suggest that depression is significantly frequently accompanied by hypertension and that about half of patients with depression accompanied by hypertension have a moderate or high risk for cardiovascular disease (eg, IHD).

Disclosure: None of the authors have any financial conflicts of interest regarding this study to disclose.

Acknowledgements: The authors would like to thank psychiatrists at Teikyo University School of Medicine for their help with the medical examinations.

References

9) Axon RN, Zhao Y, Egede LE: Association of depressive symptoms with all-cause and ischemic heart disease mortality in
当院ERにおける、うつ病と虚血性心疾患に関する後向き研究

寺倉 守之  藤崎 奄一 須田 隆裕 佐川 俊世
坂本 哲也

要旨 うつ病は、ストレスを契機として高齢者に身体化することが多いといわれており、また、それらは生活習慣病、とくに心血管疾患と関連があるといわれている。今回我々は、うつ病に関連した虚血性心疾患既往を含め、生活習慣病因子の同定を目的とした検討を行った。以前より当院メンタルヘルス受診歴があり、2009年5月〜2010年5月までに当院ERを受診したうつ病（n=269）、その他精神疾患（n=128：統合失調症n=116、不安神経症n=8、解離性障害n=4）について各背景因子（年齢、性別、血圧、心疾患歴有無、高血圧歴有無、糖尿病歴有無、脂質異常症有無、WBC、CRP）を比較検討した。いずれの検定においてもp<0.05をもって差を有意と判定した。それぞれ比較検討した結果、平均年齢（うつ病：56.5±19.4、その他：48.8±17.2歳；p<0.001）がうつ病群で高いため、年齢調整後、高血圧既往（うつ病：40.6、その他：19.7％；p=0.009）がうつ病群にて有意に高値を示した。また、多変量ロジスティック解析の結果、高血圧既往がうつ病に関して独立関連因子であった（p=0.045；オッズ比1.97，[95% CI, 1.01-3.89])。また、うつ病と合併した高血圧症例の頻度は、中等度の心血管リスクが非うつ病群に比べ有意に高かった（34.6% vs. 13.0%；p<0.001）。うつ病と高血圧症との合併例は、心血管疾患ハリスク症例として診療にあたる必要があると思われた。

（日救急医会誌. 2013; 24: 77-84）

キーワード：精神疾患、収縮期血圧、高血圧

原稿受理日：2012年4月13日（12-039）

帝京大学医学部救急医学講座

著者連絡先：〒173-8606 東京都板橋区加賀2-11-1